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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,336	12/01/2004	Philip John Birch	117-524	3696

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EXAMINER	
CAPPS, KEVIN J	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/508,336	Applicant(s) BIRCH ET AL.	
	Examiner Kevin Capps	Art Unit 1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 26 January 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: See continuation sheet. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 1-16, 19, 38, 39, 41, and 48-66.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

SPE AU 1617

Continuation Sheet from Advisory Action

1. Applicant's amendments have not been entered because they raise the issue of new matter. Specifically, there is no support in the specification for the new limitation in claim 48 that the therapeutic plasma concentration of buprenorphine is maintained for at least 6 hours. Applicant points to p. 18, l. 7, for support of the new T_{maint} limitations. However, at p. 18, ll. 5-10, there is no description of a nasal spray formulation comprising buprenorphine wherein the therapeutic plasma concentration of buprenorphine is maintained for at least 6 hours after administration. It is noted that the figures that show the therapeutic plasma concentration of buprenorphine after nasal administration only show time points out to 6 hours. Thus, there is not support for this amendment.

2. Applicant's rebuttal arguments against the rejection of claims 1-15, 38, 39, and 41 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Watts et al. (WO 98/47535), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" in Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 1. (1995) Easton, PA: Mack. pp. 613-615), and Nairn (Nairn, J. G. "Solutions, Emulsions, Suspensions and Extracts" in Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 2. (1995) Easton, PA: Mack. pp. 1495, 1496 and 1502) have been fully considered but are not persuasive. Applicant alleges that the compositions of Eriksen et al. differ from the composition of the instant claims in that dextrose is present. It is noted that the instant claim 12, which depends from claim 1,

further specifies that the compositions of the instant application comprise dextrose. Also, the formulations disclosed in the instant specification comprise dextrose. Eriksen et al. clearly teach that their formulations comprise dextrose (p. 804). Thus, there is no discrepancy in this sense.

3. Applicant goes on to state that the compositions of Eriksen et al. differ from the instantly claimed formulations comprising buprenorphine and pectins because there are no pectins in the formulations, the pH is different, there is no teaching of the absence of divalent metal cations, and there is no teaching that the formulations gel on the nasal mucosa. Regarding the pH and pectins, Watts et al. teach the herein-claimed pectins and a pH substantially close to the herein-claimed range for sustained delivery of agents on the nasal mucosa. Regarding the fact that Eriksen et al. are silent with respect to their formulations being free of divalent metal cations, the Examiner respectfully points out that a key factor in determining obviousness under § 103 is "the level of ordinary skill in the pertinent art". If the standard of the § 103 rejection was what would have been obvious to a person of no skill in the art, it might have been assumed that tap water could be used in the formulations of Eriksen et al. However, it is very well known and routine to use deionized or distilled water in scientific experiments where the presence of metal ions or other contaminants might interfere with the results, particularly for something as sensitive as a pharmaceutical formulation. Further, Watts et al. teach that using the herein-claimed pectins causes the nasal spray solutions to gel on the nasal mucosa in the absence of metal ions (Abstract). Why would the person of ordinary skill in the art assume that tap water would be used if Watts et al. teach that

nasal spray formulations incorporating their mucoadhesives in the absence of metal ions? This teaching also addresses Applicant's limitation that the instantly claimed formulations comprising the pectins of Watts et al. gel on the mucosa. Applicant also goes on to discuss the relatively high maximum plasma concentrations that are rapidly achieved and well sustained. It is noted that these are not limitations in the claims. Further, even if these were limitations in the claims, they are inherent properties of the formulation suggested by Eriksen et al. in view of Watts et al.

4. Applicant finally argues that Watts et al. teach away from a formulation with the desired properties of a rapid onset of analgesia, a closer to optimum level of analgesia, or analgesia that is well sustained because Watts et al. teach that if the formulation is for local administration, the formulation should not enhance transmucosal absorption, and if for systemic administration, the formulation should not give rise to any significant plasma concentration. Firstly, it is noted that these are not limitations in the claims. Secondly, it is pointed out that on p. 3, lines 16-25, Watts et al. teach that incorporation of the pectins into nasal spray solutions produces a simple nasal delivery system that can be used to modify (increase or decrease) the absorption characteristics when administering drugs systemically or locally. Watts et al. teach that when the drugs are to be administered locally, the system should not enhance absorption to effect increased systemic delivery. However, this is only one of the options for modulating the absorption characteristics, and it is particularly only relevant to local delivery of the drugs. Because buprenorphine is for systemic delivery, it would have been obvious to a person of ordinary skill in the art that the pectin gelling agents could be used to increase

systemic delivery of the active compounds, if desired. Also, at the Applicant-cited passage p. 14, l. 12 on, Watts et al. teach that the nasal composition can be formulated to alter (increase or decrease) the rate of transport in the general circulation, not only decrease as Applicant asserts. See also p. 14, lines 20-24, where Watts et al. teach that the "invention may thus be used for the modification of the systemic absorption of mucosally administered drugs." Also on p. 14, Watts et al. suggest that the formulation can be used for delivery of apomorphine and fentanyl, which are systemic analgesics similar to buprenorphine. Thus, Watts et al. do not teach away from systemic administration of buprenorphine with their mucoadhesives.

5. Applicant's rebuttal arguments against the rejection of claims 16 and 53-59 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1) have been fully considered but are unpersuasive. Applicant states that the composition of Eriksen et al. differs from the present formulations in that they comprise dextrose, do not contain chitosan and hydroxypropylmethylcellulose (HPMC), and have different pHs. It is noted that because of the open language "comprising" in the claims, the inclusion of dextrose in the instantly claimed formulations is not precluded. Further, the exemplified formulations in the specification comprise dextrose. Thus, the compositions of Eriksen et al. do not differ from the instantly claimed formulations in this sense.

6. Regarding the presence of chitosan and HPMC, the previous Office Action acknowledges that Eriksen et al. do not teach these additives in the formulations. This

is why the Koochaki reference was applied. Koochaki teaches the addition of the mucoadhesives chitosan and HPMC to retain the active agent in the nasal cavity for sustained delivery. Although Koockaki does teach that the formulations are in a powder form, it would have been obvious to the person of ordinary skill in the art that the mucoadhesives chitosan and HPMC could also be used in a solution that gels upon introduction into the nasal cavity to achieve sustained delivery by simply lowering the concentration of the mucoadhesives. Koochaki in fact teaches that this is a known strategy in the pharmaceutical formulation art (p. 2, lines 16-22). Koochaki does not teach that this strategy in ineffective. He merely teaches that the powder formulation is an alternative to the solution formulation that gels on the mucosa. The optimal concentration of the mucoadhesives that would allow sprayability and mucoadhesion could be arrived at through routine experimentation by the ordinary skilled artisan. Thus, it would have been obvious that the mucoadhesives they teach, chitosan and HPMC, could be used in nasal spray solutions that gel on the mucosa to achieve sustained release of the active agent. Regarding the pH of the compositions, it was noted in the previous Office Action that Koochaki teaches a pH of 4.5, which is within the herein-claimed range.

7. Applicant's rebuttal arguments against the rejection of claims 19 and 60-66 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195) have been fully considered but are unpersuasive. Applicant argues that the ordinary skilled artisan would not be motivated to combine of

Eriksen et al. and Williams et al. to arrive at the instantly claimed invention because Williams et al. is directed to local delivery of analgesics, whereas the instantly claimed formulations are for systemic delivery of the analgesic. It is noted that the intended use of the composition does not lend patentability to the composition. Williams et al. exemplify buprenorphine as a suitable opioid for formulation with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 4, lines 11-13). Regardless of whether the formulation is for systemic or local administration of the buprenophine, the compositions are identical. Eriksen et al. teach that introduction of buprenorphine into the nasal cavity achieves systemic delivery of the active agent for inducing analgesia. Thus, the person of ordinary skill in the art would understand that using the excipients of Williams et al. in a nasal spray solution containing buprenorphine would achieve sustained systemic delivery of the agent through the nasal mucosa, as opposed to sustained local delivery through the buccal mucosa. Finally, Williams et al. teach that chitosan can also be incorporated with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 7, ll. 10-11).

8. Regarding the rejection of claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 on the ground of nonstatutory obviousness-type double patenting over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917, Applicant argues that there is no teaching of "formulations for the nasal cavity that comprise buprenorphine or a salt thereof". As pointed out in the previous Office Action, '917 teaches a composition adapted for nasal delivery comprising a methane sulphonate salt of an opioid analgesic (claims 1). At col. 3, ll. 21-25, buprenorphine is exemplified as an opioid analgesic for incorporation into

the nasal delivery formulation. Thus, '917 teaches "formulations for the nasal cavity that comprise buprenorphine or a salt thereof".